REMARKS

Applicants have amended claims 41, 42 and 46 such that they refer only to molecules that induce or inhibit angiogenesis. Applicants have amended the claims without acknowledging in any sense that the cancelled subject matter is not patentable and expressly reserving the right to pursue the cancelled subject matter in one or more continuation applications.

The claims of this application stand rejected under one or more of 35 U.S.C. §112, first paragraph, 35 U.S.C. §102 or §103. Applicants respectfully disagree.

THE REJECTION UNDER 35 U.S.C. §112, 1ST PARAGRAPH PURPORTED LACK OF ENABLEMENT

Claims 41, 42, 44, 46 and 47 stand rejected under 35 U.S.C. §112, first paragraph, for purportedly lacking enablement.

The Examiner acknowledges that the claims are enabling for a method of introducing an AAV vector expressing an angiogenic protein, such as FGF protein and VEGF protein, into cardiomyocytes via intracoronary injection so as to ameliorate the symptom of heart disease. Nonetheless, the Examiner continues to contend that the claims are not enabled for a method of introducing an AAV vector expressing any protein or antisense RNA other than angiogenic protein into cardiomyocytes via intracoronary injection so as to provide therapeutic effect in vivo for a particular disease, such as heart disease. "The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 9-10-03." (Office Action page 2). In view of applicants' amendments to the claims such that they relate only to antisense molecules and proteins capable of inducing or inhibiting angiogenesis, applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph for purported lack of enablement.

> "A decision on the issue of enablement required determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue

> experimentation. It is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification."
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> *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ 1321, 1329 (Fed. Cir. 1990)

The present claims are directed to a specific delivery method of introducing a protein or a nucleic acid molecule capable of inducing or inhibiting angiogenesis into cardiomyocytes using rAAV at dosages determined to provide stable and efficient transduction of those cells. Amended claim 46 indicates that a particular cardiovascular effect, inducing angiogenesis or inhibiting angiogenesis, is achieved but does not indicate the particular level or degree of that effect. Claim 47 specifies that the anti-sense RNA is capable of inducing angiogenesis or is capable of inhibiting angiogenesis.

According to the Examiner, the rejected claims prior to the amendment made herein lack enablement because of the unpredictability of gene therapy, which the Examiner contends is the specification's failure to actually demonstrate that each and every indicated molecule encompassed by those claims "provide therapeutic effect for a particular cardiovascular disease or condition in a patient in vivo" (September 9, 2003 Office Action, sentence bridging pages 4-5). However, this is not the standard against which to assess enablement. Moreover, the Examiner's contention is not applicable to the present scope of the amended claims. The amended claims provide a method wherein a rAAV encoding a particular molecule capable of inducing or inhibiting angiogenesis (e.g, thymidine kinase, p27 and the like) is introduced into cardiomyocytes using the claimed infusion route. Given that markers and angiogenic proteins such as FGF-5 and VEGF, can be introduced by the claimed method, one of skill in the art would reasonably expect that other molecules capable of inducing or inhibiting angiogenesis could also be introduced by the same infusion method to achieve stable and efficient transduction and that this could be done without undue experimentation: Undue experimentation is the standard against which to assess enablement.

Applicants have provided declaratory evidence of record from a prominent expert in the gene therapy field, Dr. Michael Parmacek, that applicants have enabled those of skill in the art to practice the claimed invention without undue experimentation. Dr. Parmacek's declaration states

that as of December 1998 many cloned DNA molecules encoding angiogenic factors were readily available, e.g., acidic FGF, basic FGF, FGF-5. Platelet-derived growth factor (PDGF), angiogenin and vascular endothelial growth factor (Parmacek Declaration ¶12). The Parmacek Declaration also states that prior to December 1998, several groups had demonstrated the in vivo transduction and expression of rAAV vector in rodent cells, in particular the intraventricular or intracardiac injection of rAAV vector encoding an antisense RNA for antiotensinogen receptor (AT1-R) and demonstrated expression of the rAAV vector as evidenced by a reduced blood pressure and a slowed development of hypertension in rats (Parmacek Declaration ¶17). Dr. Parmacek also states that prior to December 1998 the alkaline phosphatase (AP) reporter gene was expressed in the carotid adventitia of cynomolus monkeys using rAAV vectors infused or injected into the corotid artery (Parmacek Declaration ¶18) The foregoing demonstrates that the art of gene transfer and expression was not undeveloped and unpredictable. Rather the foregoing demonstrates that one of skill in the art would be able to practice applicant's invention without undue experimentation thus satisfying the requirements of 35 U.S.C. 112, first paragraph.

The Examiner contends that the Parmacek Declaration is unpersuasive for the reasons of record in the preceding 9-10-03 Office Action, in particular because of the supposed "unpredictability of the art of gene therapy" (9-10-04 Office Action Page 7). Applicants disagree with the Examiner's comments that the Parmacek Declaration is unpersuasive as to the enablement of the canceled subject matter for the reasons already of record. Nonetheless applicants have amended claims 41, 42 and 46 such that they relate only to inducing or inhibiting angiogenesis. The Examiner acknowledges that applicants' method for introducing an AAV vector expressing an angiogenic protein into cardiomyocytes is enabled:

> "....the specification, while being enabling for a method of introducing an AAV vector expressing an angiogenic protein such as FGF protein and VEGF protein, into cardiomyocytes via intracoronary injections so as to ameliorate the symptom of heart disease as disclosed by Hammond et al., 1998 (WO 98/50079), does not reasonably provide enablement for a method of introducing an AAV vector expressing any protein or antisense RNA other than angiogenic protein into cardiomyocytes via intra coronary injection ...." (Office Action page 2).

While applicants disagree with the Examiner's contention supra that Hammond et al. discloses introducing an AAV vector expressing an angiogenic protein, such as FGF protein and VEGF protein, into cardiomyocytes via intracoronary injections, applicants agree that the specification is enabling for a method of introducing an AAV vector expressing an angiogenic protein into cardiomyocytes via intracoronary injections. Applicants' amended claims relate to antisense molecules and to proteins that induce or inhibit angiogenesis and as such the amended claims are enabled by the application.

The Examiner states that the specification fails to provide adequate guidance and evidence whether the desired molecule would be expressed and be present in a sufficient amount at the targeted site such that the desired molecule could provide therapeutic effect for a particular cardiac disease or condition in a patient *in vivo*. It is respectfully submitted that the specification teaches that molecules competent to induce angiogenesis and anti-angiogenesis factors can be administered to treat or ameliorate cardiovascular conditions. The specification discloses many angiogenic factors, e.g., FGF-1, FGF-2, FGF-5, VEGF, or HIF-1 (page 5, lines 24-25) that are useful in this invention (page 5, lines 12-14 and page 5, lines 24-26). Applicants have also demonstrated the successful transduction of cardiomyocytes by infusing the coronary artery with a rAAV.

Thus, one of ordinary skill the art, with applicants' specification in hand and without undue experimentation, could stably and efficiently transduce cardiomyocytes with an rAAV, comprising a nucleic acid molecule encoding an antisense molecule or a protein capable of inducing or inhibiting angiogenesis, by infusing a coronary artery and would expect to obtain sufficient expression of the antisense molecule or protein to induce or inhibit angiogenesis in a subject *in vivo*.

In conclusion and based on the foregoing, the specification together with the state of art at the time of filing, provided one of skill in the art with sufficient guidance to make and use the full scope of the claimed invention without requiring undue experimentation. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

THE REJECTION UNDER 35 U.S.C. 102

Claims 24, 32, 33, 40, 43 and 45 stand rejected for purportedly being anticipated by Hammond et al. (WO 98/50079, hereinafter "Hammond"). Applicants respectfully disagree and in view of the following remarks request that the Examiner reconsider and withdraw the rejection.

> Anticipation under 35 U.S.C. §102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention.
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> *Electro Med. Sys. S.A. v. Cooper Life Sciences*,
> 32 USPQ2d 1017, 1019 (Fed. Cir. 1994).

It is well-established that an anticipatory reference must recognize each and every element of a claimed invention. Hammond fails to teach each and every limitation of the claimed invention and as such fails to satisfy the requirements of 35 U.S.C. §102.

Applicants claims relate to a method for achieving stable and efficient transduction of cardiomyocyts. The claimed method requires a specific dosage of AAV (IU/gm) to be administered to a subject and requires that the AAV be administered for a time sufficient to achieve stable and efficient transduction of cardiomyocytes. Hammond teaches transient transduction of cardiomyocytes and does not teach the administration of the particular dosage of AAV recited in applicants' claims to achieve stable and efficient transduction.

The Examiner states: "Hammond teaches administering 1.5×10^{12} adenovirus particles to Yorkshire domestic pig via intracoronary injection (e.g. p55, 63)."(Office Action, page 8, lines 5-7) Applicants agree. Hammond teaches the injection of adenovirus (e.g. Hammond page 55 and 63), but Applicants claims recite AAV, not adenovirus. As such the cited text does not teach each and every limitation of applicants' claims and therefore fails to support a rejection under 35 U.S.C. §102.

The Examiner has speculated on the dosage of adenovirus in IU/gm that Hammond might have administered to a Yorkshire domestic pig, if the pig weighed, according to the Examiner, 50-150 kg. But Hammond does not teach one of skill in the art to consider the pig's weight

when determining the appropriate dosage of virus: That knowledge comes from applicant's own specification wherein they teach that the weight of the subject is to be considered. Without Applicant's specification in hand, the Examiner would not have had any motivation to make her calculation.

The Examiner states:

> Hammond teaches a method for treating patient with congestive heart failure by delivering a virus vector, such as rAAV vector, expressing FGF or VEGF to said patient via direct intracoronary injection of said vector into coronary arteries in an amount of 10^6-10^{14} particles (see page 69, claims 26 and 28-30).
>
> (Office Action page 8, lines 9-13.)

The Examiner further contends

> ...in claims 26 and 28-30 Hammond not only teaches delivering adenovirus vector but also teaches delivering the recited dosages of rAAV vector expressing FGF or VEGF to a patient.
>
> (Office Action page 8, penultimate sentence).

However, the Examiner has mischaracterized the teachings of Hammond's claims 26 and 28-30 which appear on page 69. First, none of the cited claims recite FGF or VEGF. Secondly, none of the claims recite particular amounts of AAV and lastly none of the claims recite the stable and efficient transformation of cardiomyocytes.

Applicants claims require a specific amount of AAV to be administered to a subject and require the AAV to be administered for a time sufficient to achieve stable and efficient transduction of cardiomyocytes. Contrary to the Examiner's contention, Hammond's claims 26 and 28-30 demonstrate that Hammond fails to teach all the limitations recited in applicants' claims.

Hammond claim 26 recites

26. The method of claim 25, wherein the vector is a viral particle.

Hammond claim 25 states that the vector is a "viral vector or a lipid-based vector" and depends on claim 1. Claim 1 refers to a "vector" but does not identify the vector, does not refer to any amounts of vector and does not refer to the "stable and efficient" transduction of cardiomyocytes, as are recited in applicants' claims.

Hammond claim 28 recites:

28. The method of claim 26, wherein the viral particle is a replication-defective adeno associated virus (AAV).

The combination of claims 1, 25 and 26 fail to teach particular dosages of AAV per gram of subject and fail to teach the "stable and efficient" transduction of cardiomyocytes.

Hammond claims 29 and 30 recite:

29. The method of claim 26, wherein about 10^6 to 10^{14} virus vector particle are delivered in the injection.

30. The method of claim 27 wherein about 10^8-10^{12} adenovirus vector particle are delivered in the injection.

Neither claim 29 or 30 recite AAV or depend from a claim that recites AAV. Claims 29 and 30 depend on claims 26 and 27 respectively: neither claim 26 or 27 teach AAV: Claim 26 simply states a "viral vector" and claim 27 is expressly adenovirus specific.

Not only do Hammond's claims 26 and 28-30 fail to teach "delivering the recited dosages of rAAV vector expressing FGF or VEGF to a patient" as stated by the Examiner, Hammond's claims clearly fail to teach a method for the stable and efficient transformation of cardiomyocytes.

The foregoing remarks demonstrate that Hammond fails to teach "each and every limitation of a claimed invention" as is required by 35 U.S.C. §102 and therefore does not anticipate applicants' invention as claimed. As such, applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 102.

THE REJECTION UNDER 35 U.S.C. 103

Claims 24-30 and 35-39 stand rejected under 35 U.S.C. § 103 for purportedly being unpatentable over Hammond. Applicants respectfully disagree.

The Examiner states that Hammond suggests using 10^8 to 10^{12} rAAV particles. As discussed *supra*, this is not an accurate statement. Hammond suggests using 10^8 to 10^{12} recombinant adenovirus particles, Hammond does not suggest the dosage of rAAV virus particles. The Examiner also states

> "one of ordinary skill in the art at the time of the invention would have been motivated to use 10^8-10^{12} rAAV particles as taught by Hammond for transduction of cardiomyocytes because when lower dosage of rAAV particles results in lower transduction efficiency one would use higher dosage of rAAV particles and expect higher transduction efficiency would be obtained." (Office Action page 10).

However, the Examiner has failed to evaluate Hammond for all that it teaches, as is required to support a proper rejection under 35 U.S.C. §103.

> The cited art must be considered for all that it teaches and the Examiner is not permitted to pick and choose from those teachings only so much that would render the claims obvious.
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> *ATD Corp. v. Lydall, Inc.* 48 USPQ2d 1321 (Fed. Cir. 1998)

Applicants claimed method is for the stable and efficient transformation of cardiomyocytes by infusing a specific dose of recombinant AAV for a sufficient time to achieve stable and efficient transformation of cardiomyocytes. Hammond teaches against stable transformation of cardiomyocytes by stating:

> "In fact, for the present purposes, transient expression is generally desirable over stable integration from the perspective of safety since disruption of the host can be avoided. As the experimental examples below demonstrated, transgene expression was maintained sufficiently long to allow collateral vessel development and concomitant restoration of normal heart function. Thus the angiogenic factor gene does not have to be present in the transfected cell for more than a few weeks to produce a therapeutic effect. (Hammond page 22 line 33 to page 23 line 4)

Thus not only does Hammond fail to teach or suggest the claimed method as discussed *supra* and in applicants' previous responses, Hammond actually teaches against stable transformation of cardiomyocytes. Therefore, one of skill in the art would not be motivated by

Hammond to stably transduce cardiomyocytes with any vector, much less stably transduce cardiomyocytes with particular dosages of AAV.

The Examiner contends that Hammond teaches a specific amount of virus particles, such as 1.5×10^{12} for delivery via intracoronary injection. However, Hammond only teaches administering this total amount of virus in the context of Adenovirus and in the context of transient expression. Hammond does not teach or suggest administering an amount of any virus necessary to achieve stable transduction of cardiomyocytes. Without such a teaching or suggestion, Hammond fails to provide one of skill in the art with the guidance necessary to achieve stable and efficient transduction of cardiomyocytes with AAV.

In sum, Hammond does not teach or suggest transducing cardiomyocytes with a particular dosage of AAV and actually teaches against stable transduction of cardiomyocytes in general. As such one of skill in the art upon reading Hammond for all that it teaches would not be motivated to design a method, such as applicants, wherein AAV is administered to a subject at a particular dose in IU/gm to obtain stable and efficient transduction of cardiomyocytes. As such, Hammond fails to render applicants' claims obvious.

In view of the foregoing, applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims for purportedly being obvious over Hammond.

Applicant believes that no additional fees are required for the filing of this Response. However, the Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 06-2375, under Order No. BSX 234 US/10408799. A duplicate copy of this paper is enclosed.

Respectfully submitted,

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